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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) 56908(71699)	
	Application Number 10/507,466-Conf. #1259	Filed September 10, 2004
	First Named Inventor Marc A. Ostermeier	
	Art Unit 1632	Examiner S. L. Chen

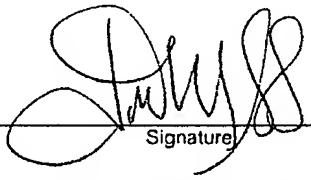
Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 53,624
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____



Signature

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August 7, 2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [ ] *Total of 1 forms are submitted.

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Docket No. 56908 (71699))

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Marc Ostermeier	CONF. NO.:	1259
U.S. SERIAL NO:	10/507,466	EXAMINER:	Shin-Lin CHEN
FILED:	September 10, 2004	GROUP:	1632
FOR:	MOLECULAR SWITCHES AND METHODS FOR MAKING AND USING THE SAME		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REMARKS: PRE-APPEAL BRIEF REQUEST FOR REVIEW

The following remarks support Applicants' "Pre-Appeal Brief Request for Review" filed herewith in the above-referenced application. These remarks constitute no more than five pages, and are being filed with a Notice of Appeal, thereby satisfying the requirements.

Claims 45 - 47 were rejected under 35 USC §112, first paragraph, for failing to comply with the enablement requirement. Claims 1 – 5, 7, 8 and 14 were rejected under 35 USC §102(b) as being anticipated by Lacatena et al. (PNAS, Vol. 91, pp.10521 – 10525. 1994). Claims 1 – 5, 7, 8 and 14 were rejected under 35 USC §102(e) as being anticipated by Anderson et al. (US Patent No. 6,596,485). Claims 1 – 5, 7, 8 and 14 were rejected under 35 USC §102(b) as being anticipated by Manoil et al. (J of Bacteriology vol. 172, No. 2 p.515 - 518). Claims 1 – 5, 7, 8 and 14 were rejected under 35 USC §102(b) as being anticipated by Mountford et al. (TIG, Vol 11). Claims 1 – 5, 7, 8 and 14 were rejected under 35 USC §102(e) as being anticipated by Ong et al. (US Patent No. 6,687,035). Claims 1 and 45 - 47 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Anderson et al. (as above), in view of Norris, 2006 (US Patent No. 7,135,176). The foregoing rejections are respectfully traversed.

Applicants respectfully request review of the Final Office Action in the above-referenced application. No amendments are being filed with this request.

Applicants are filing the "Pre-Appeal Brief Request for Review" based on the following errors in the Final Office Action, mailed February 9, 2009.

The Examiner has made clear errors because none of the Lacatena, Anderson, Manoil, Mountford, or Ong references, or the combination of the Anderson reference and the Norris reference together, teaches or suggests a modulatable molecule, comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state, thereby generating a nucleic acid fusion molecule, as currently claimed.

The Examiner incorrectly relies on the publications and the argument that each cited reference teaches an insertion sequence and an acceptor sequence that "are separate before fusion and a new state is formed when both...(are) fused together." (Office Action dated 6/12/2009). The Examiner incorrectly relies on the publications and the assertion that "a fusion protein can respond to a stimulant or inhibitor, therefore, **any fusion protein is a modulatable molecule**" (Office Action dated 6/12/2009, emphasis added).

The claimed invention requires that the state of the polypeptide encoded by the acceptor nucleic acid is coupled to the state of the polypeptide encoded by the insertion nucleic acid molecule, or the state of the polypeptide encoded by the insertion nucleic acid is coupled to the state of the polypeptide encoded by the acceptor nucleic acid. Thus, according to the present invention, a change in state in either the insertion sequence or acceptor sequence will result in a change in state of respective other portion of the fusion. (see, e.g. page 17, line 20). For example, when an enzyme (insertion) and a ligand binding protein (acceptor) each encode a state, the state of the polypeptide encoded by the ligand binding protein (acceptor) is coupled to the state of the polypeptide encoded by the enzyme (insertion), or the state of the polypeptide encoded by the enzyme (insertion) nucleic acid is coupled to the state of the polypeptide encoded by the ligand binding protein (acceptor) nucleic acid. This is exemplified in Applicant's Example 1, where *E. coli* maltose binding protein ("MBP") is the acceptor polypeptide sequence and penicillin-hydrolyzing enzyme TEM1 β-lactamase is the insertion polypeptide sequence, and each have activity on their own (i.e. each encode a state) and the fusion protein modulates β-lactamase activity through changes in maltose concentration (i.e., the fusion protein behaves as an allosteric enzyme).

The specification describes "an insertion sequence" at page 14, line 13, and "Coupled" at page 13, beginning at line 29. Moreover, the specification described a "state" at page 3, line 10 as comprising "its ability or latent ability to emit or absorb light, its ability or latent ability to change

conformation, its ability or latent ability to bind to a ligand, to catalyze a substrate, transfer electrons, and the like. Preferably, molecular switches according to the invention are multistable, i.e., able to switch between at least two states."

Regarding the Lacatena reference, the Examiner argues that generation of the huß 2AR-phoA fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and...couples the state of the insertion sequence to the state of the acceptor sequence. (Office Action dated 6/12/2009). The Lacatena reference analyzes the assembly of the huß2 AR membrane protein by using of huβ2 AR-PhoA fusions to determine membrane topology and insertion. Lacatena use the PhoA activity of the fusion proteins to determine if the huβ2 AR-PhoA fusions have acquired the correct topology. Lacatena teaches assaying the alkaline phosphatase activity of the fusion protein, where the fusions retain the function of the inserted protein. Lacatena does not teach a modulatable molecule as claimed, where the state of the insertion sequence is coupled to the state of the acceptor sequence.

The Anderson reference provides fusions of green fluorescent protein (GFP) and random peptides, and teaches a fusion nucleic acid comprising a first nucleic acid encoding a GFP scaffold protein, a second nucleic acid encoding a linker fused to the C-terminus of the scaffold protein and a third nucleic acid encoding a random peptide fused to the C-terminus of the linker. The GFP and the second and third nucleic acids do not each comprise a state such that the state of one is coupled to the state of another .

The Manoil reference is directed to alkaline phosphate fusions that are used as sensors of subcellular location. Manoil describe TnphoA transposons that are used to generate gene fusions encoding hybrid proteins. Manoil et al. describe that "the basis of the alkaline phosphatase fusion approach is that finding the activity of the enzyme response differently to different environments (and) the activity of the fusion protein gives evidence as to its location." (p.517). Manoil et al. are using alkaline phosphatase as a reporter. The Examiner argues that "(g)eneration of the hybrid proteins constitutes insertion of an insertion sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence (and) the resulting hybrid protein or gene encoding said hybrid protein is a new state." (Office Action dated 6/12/2009).

The Mountford reference is directed to the use of IRES elements in transgenic expression constructs to create polyfunctional RNAs. An IRES is a nucleotide sequence that allows for translation initiation in the middle of a messenger RNA (mRNA) sequence. Mountford describe various uses of IRES elements or IRES-selectable marker cassettes, for example in coexpression of counter selectable markers (p. 180), in cloning vectors (expression cloning, two-hybrid cloning) and in transgene expression vectors (p.181) and in gene targeting vectors (p.182). The Examiner argues that "(t)he gene trap vector is an insertion sequence and the chromosomal transcription units are acceptor sequences (and) the gene trap vector encodes betagal protein and the chromosomal transcription until encodes another protein...(t)he resulting fusion molecule is a new state." (Office Action dated 6/12/2009).

The Ong reference is directed to a gene trap DNA construct comprising two functional units, where the first functional segment consists of a mutagenic, detectable component that comprises an unpaired splice acceptor sequence fused to an internal ribosomal entry sequence (IRES) linked to a reporter gene followed by a polyadenylation signal sequence. The second functional unit encodes a selectable sequence acquisition module consisting of a promoter that is actively transcribed in ES cells, fused to a reporter followed by an unpaired synthetic consensus splice donor sequence. The Examiner argues that the Ong reference "teaches that (a) gene trap DNA construct is an insertion sequence and the ES cell genome is acceptor sequence. The gene trap DNA encodes a reporter and the trapped gene in ES cell genome encodes another protein (and) the resulting fusion is a new state." (Office Action dated 6/12/2009). The Examiner incorrectly asserts that "a fusion protein can respond to a stimulant or inhibitor, therefore, any fusion molecule is a modulatable molecule." (Office Action dated 6/12/2009).

In characterizing the Anderson, Manoil, Mountford and Ong references, the Examiner incorrectly asserts that any fusion protein is a modulatable molecule. Simply because two sequences are fused does not make the resulting fusion molecule modulatable as claimed.

The Anderson reference, as discussed above, fails to teach assembling a modulatable molecule as claimed. The Norris reference does not cure the defects of the Anderson reference. The Norris reference is directed, in part, to immunogenic compositions and recombinant VMP-like genes useful for treatment and diagnosis of Lyme disease. In the Office Action mailed 5/20/2008, the Examiner argues that "Norris teaches random cloning of lambda.DASH-Bbl2 insert by treating

purified bacteriophage DNA with DNAseI in the presence of Mn2+ and cloned into EcoRV-digested pBluescript IISK." Nowhere in the Norris reference is there teaching or suggestion of a modulatable molecule, as claimed. Therefore, the teachings of the cited art, when combined, do not result in the claimed invention.

The Examiner has maintained the rejection of claims 45 - 47 under 35 USC §112, first paragraph, for allegedly failing to comply with the enablement requirement. The specification provides ample guidance to perform the method as claimed. Applicants refer to the specification at paragraph [0021], paragraph [0130], where a number of different strategies can be used to create the fusion molecules of the instant invention, including nuclease treatment, mechanical shearing, chemical treatment or radiation treatment. Applicants refer to paragraph [0140] of the application that teaches "it should be obvious to those of skill in the art that any method of introducing breaks into a DNA molecule can be used (e.g., such as digestion by mung bean nucleases, endonucleases, restriction enzymes, exposure to chemical agents, irradiation, and/or mechanical shearing)." Applicants refer to particular examples in the specification that teach construction of random insertion libraries using strategies including nuclease treatment, mechanical shearing, chemical treatment or radiation treatment, for example beginning at paragraph [0139], and generation of conditional heterodimers with exonuclease at paragraph [0170], construction of random insertion libraries at paragraph [0216], construction and characterization of insertion libraries at paragraph [0222], among others.

Accordingly, Applicants submit that all of the claims under final rejection are in condition for allowance and should be allowed, and that the Final Office Action should be withdrawn.

Respectfully submitted,

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Date: August 9, 2009
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